Amendments To The Specification

The paragraph beginning at page 1, line 24, is amended as follows:

In fact, the Food and Drug Administration has approved the therapeutic use of one such anti-CD20 antibody, ~~Rituxan®~~ RITUXAN®, for use in relapse and previously treated low-grade non-Hodgkin's lymphoma (NHL). Also, the use of ~~Rituxan®~~ RITUXAN® in combination with a radiolabeled murine anti-CD20 antibody has been suggested for the treatment of B cell lymphoma.

The paragraph beginning at page 2, line 3, is amended as follows:

However, while anti-CD20 antibodies and, in particular, ~~Rituxan®~~ RITUXAN® (U.S.; in Britain, ~~MabThera®~~ MABTHERA®; in general ~~Rituximab®~~ rituximab), have been reported to be effective for treatment of B-cell lymphomas, such as non-Hodgkin's lymphoma, the treated patients are often subject to disease relapse. Therefore, it would be beneficial if more effective treatment regiments could be developed.

The paragraph beginning at page 4, line 3, is amended as follows:

While any anti-CD20 antibodies can be used for the methods of the present invention, a preferred chimeric antibody is C2B8 (IDEC Pharmaceuticals, ~~Rituximab®~~ rituximab). A preferred radiolabeled antibody is Y2B8, which is a murine antibody labeled with yttrium-90 (^{90}Y). However, antibodies with other radiolabels may be used, particularly those labeled with a beta or alpha isotope. Anti-CD19 antibodies may also be used.

The paragraph beginning at page 4, line 15, is amended as follows:

Antibody treatments performed initially to which patients are refractory or have relapsed may include initial treatments with chimeric antibodies or mammalian antibodies. Also encompassed are initial treatments with other antibodies, including anti-CD19 antibodies and anti-Lym antibodies, and treatments with antibodies labeled with cytotoxic moieties, such as toxins, and radiolabels, e.g., ~~Oncolym®~~ ONCOLYM® (Techniclone) or Bexxar (Coulter).

The heading beginning at page 8, line 20, is amended as follows:

~~Rituximab®~~ Rituximab and Y2B8

The paragraph beginning at page 9, line 4, is amended as follows:

~~Rituximab®~~ Rituximab is one of a new generation of monoclonal antibodies developed to overcome limitations encountered with murine antibodies, including short half-life, limited ability to stimulate human effector functions, and immunogenicity (2,3).

The paragraph beginning at page 9, line 9, is amended as follows:

~~Rituximab®~~ Rituximab is a genetically engineered monoclonal antibody with murine light-and heavy-chain variable regions and human gamma I heavy-chain and kappa light-chain constant regions. The chimeric antibody is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids and has an approximate molecular weight of 145 kD. ~~Rituximab®~~ rituximab is more effective than its murine parent in fixing complement and mediating ADCC, and it mediates CDC in the presence of human complement (4). The antibody inhibits cell growth in the B-cell lines FL-18, Ramos, and Raji, sensitizes chemoresistant human lymphoma cell lines to diphtheria toxin, ricin, CDDP, doxorubicin, and etoposide, and induces apoptosis in the DHL-4 human B-cell lymphoma line in a dose-dependent manner (5). In humans, the half-life of the antibody is approximately 60 hours after the first infusion and increases with each does to 174 hours after the fourth infusion. The immunogenicity of the antibody is low; of 355 patients in seven clinical studies, only three (<1%) had a detectable anti-chimeric antibody (HACA) response.

The paragraph beginning at page 9, line 23, is amended as follows:

~~Rituximab®~~ Rituximab was genetically engineered using the murine 2B8 antibody. The 2B8 antibody has also been conjugated to different radiolabels for diagnostic and therapeutic purposes. To this end, copending application Serial Nos. 08/475,813, 08/475,815 and 08/478,967, herein incorporated by reference in their entirety, disclose radiolabeled anti-CD20 conjugates for diagnostic "imaging" of B-cell lymphoma tumors before administration of therapeutic antibody. "In2B8" conjugate comprises a murine monoclonal antibody, 2B8, specific to human CD20 antigen, that is attached to Indium[111] (^{111}In) via a bifunctional chelator, i.e., MX-DTPA (diethylenetriaminepentaacetic acid), which comprises a 1:1 mixture of 1-isothiocyanatobenzyl-3-methyl-DTPA and 1-methyl-3-isothiocyanatobenzyl-DTPA. Indium-[111] is selected as a diagnostic radionuclide because it emits gamma radiation and finds prior usage as an imaging agent.

The paragraph beginning at page 12, line 10, is amended as follows:

In addition, U.S. Patent No. 5,736,137, herein incorporated by reference, discloses sequential administration of ~~Rituxan®~~ RITUXAN®, a chimeric anti-CD20 antibody, with both or either indium-labeled or yttrium-labeled murine monoclonal antibody. Although the radiolabeled antibodies used in these combined therapies are murine antibodies, initial treatment with chimeric anti-CD20 sufficiently depletes the B-cell population such that the HAMA response is decreased, thereby facilitating a combined therapeutic and diagnostic regiment.

The paragraph beginning at page 12, line 17, is amended as follows:

Thus, in this context of combined immunotherapy, murine antibodies may find particular utility as diagnostic reagents. Moreover, it was shown in U.S. Patent No. 5,736,137 that a therapeutically effective dosage of the yttrium-labeled anti-CD20 antibody following administration of ~~Rituxan®~~ RITUXAN® is sufficient to (a) clear any remaining peripheral blood B-cells not cleared by the chimeric anti-CD20 antibody; (b) begin B-cell depletion from lymph nodes; or (c) begin B-cell depletion from other tissues.

The title of the table at page 14, line 2, is amended as follows:

~~Rituximab®~~ Rituximab: Summary of Efficacy results

The paragraph beginning at page 17, line 3, is amended as follows:

Administration of ~~Rituximab®~~ rituximab resulted in a rapid and sustained depletion of B-cells. Circulating B-cells were depleted within the first three doses with sustained depletion for up to six to nine months post-treatment in 83% of patients. Median B-cell levels returned to normal by 12 months following treatment. Although median NK cell counts remained unchanged, a positive correlation was observed between higher absolute NK cell counts at baseline and response to ~~Rituximab®~~ rituximab (10).

The paragraph beginning at page 18, line 5, is amended as follows:

Nevertheless, responses were seen with ~~Rituximab®~~ rituximab in 43% of patients with tumors > 5 cm and in 35% of patients with tumors > 7 cm, suggesting that treatment of patients with bulky disease with ~~Rituximab®~~ rituximab is feasible. This is surprising considering it was long thought that antibody therapy is not conducive to treating bulky disease due to the compact nature of the tumors.

The paragraph beginning at page 18, line 15, is amended as follows:

Because ~~Rituximab®~~ rituximab serum levels and response were positively correlated in previous studies, a Phase II study of eight weekly doses of 375 mg/m^2 ~~Rituximab®~~ rituximab was conducted in low-grade or follicular NHL patients. The ORR was 60% in evaluable patients, with a 14% CR and a 46% PR rate. Median values for TTP in responders and DR were 13.4+ months and 19.4+ months, respectively (13). Though it is difficult to compare across studies, it appears that TTP and DR may be improved by using more doses.

The paragraph beginning at page 18, line 22, is amended as follows:

Contrary to early assumptions about antibody therapy being useful only in micrometastatic disease, ~~Rituximab®~~ rituximab is quite active in high bulk disease. In a separate study, 31 patients with relapsed or refractory, bulky low-grade NHL (single lesion of > 10 cm in diameter) received 375 mg/m^2 ~~Rituximab®~~ rituximab as four weekly infusions. Twelve of 28 evaluable patients (43%) demonstrated a CR (1, 4%) or PR (11, 39%)(14).

The paragraph beginning at page 19, line 9, is amended as follows:

A report on seven patients with Waldenstrom's macroglobulinemia where the patients were treated with ~~Rituximab®~~ rituximab (375 mb/m^2 weekly times 4)(15) noted responses in 4 (57%) of patients. Median progression-free survival was 8 months (range 3 - 27+ months). Thus, ~~Rituximab®~~ rituximab should be useful in combined therapeutic protocols, particularly with chemotherapeutic reagents such as 2CdA.

The paragraph beginning at page 19, line 15, is amended as follows:

CLL is the liquid (leukemic) equivalent of small lymphocytic lymphoma (SLL). Patients with SLL had lower serum levels and a lower response rate when treated with the standard dose of ~~Rituximab®~~ rituximab than patients with other low-grade NHL subtypes. This is probably due to the very high level of circulating tumor cells in patients with CLL, and because malignant cells involved in CLL are thought to have reduced levels of expression of CD20 on the cell surface.

The paragraph beginning at page 19, line 21, is amended as follows:

Nevertheless, the present inventors have discovered that hematologic malignancies such as CLL may be treated with ~~Rituximab®~~ rituximab. A recent clinical study evaluated treatment of CLL patients at higher doses of ~~Rituximab®~~ rituximab (16). All patients receive a first dose of 375 mg/m^3 to minimize infusion-relapsed side effects. Subsequent weekly

dosages (3) remained the same but were given at an increased dose level. Sixteen patients have been treated at dosages of 500-1500 mg/m^3. Medium age was 66 years (range, 25-78). Eighty-one percent had end-stage III-IV disease. Medium white blood cell count was 40 x 10^9/L (range, 4-200), Hgb 11.6 g/dl (range, 7.7-14.7), platelets 75 x 10^9/L (range, 16-160), median numbers of prior therapies was 2.5 (range 1-9). Sixty percent of patients were refractory to treatment. Two patients developed severe hypertension with the first dose (375 mg/m^3); another one received further therapy. Toxicity at subsequent escalated dosages has been mild although no patient at the 1500 mg/m^3 dose level has been fully evaluated. Eight patients have completed therapy (4 at 500 mg/m^3, 3 at 650 mg/m^3, 1 at 825 mg/m^3). One patient treated at 560 mg/m^3 achieved full remission. One patient has progressive lymphocytosis on treatment and all other patients had reduction in peripheral blood lymphocytosis but less effect on lymph nodes. Dose escalation studies are ongoing.

The paragraph beginning at page 20, line 23, is amended as follows:

Thus, by administering certain cytokines to CLL patients prior to or concurrently with administration of ~~Rituximab®~~ rituximab, the expression of CD20 on the surface of malignant B-cells may be upregulated, thereby rendering CD20, as well as other cell surface markers such as CD19, a more attractive target for immunotherapy. A collaborative study has been initiated to test for optimal cytokine doses for CD20 upregulation in vivo. The study protocol involves treating ten patients initially with GM-CSF at 250 mcg/m^2 SQ QD X 3, ten patients with IL-4 mcg/kg SQ QD X 3, and ten patients with G-CSF at 5 mcg/kg SQ QD X 3. Mononuclear cells will be separated by Ficon Hypaque centrifugation for apoptotic studies to determine if upregulation of CD20 translates to enhanced killing of tumor cells by ~~Rituximab®~~ rituximab.

The paragraph beginning at page 21, line 23, is amended as follows:

Hence, anti-CD20 antibody therapy will be particularly useful for patients who are refractory or who have relapsed after treatment with chemotherapeutic drugs. ~~Rituximab®~~ rituximab therapy may also be combined with radiotherapy in these patients. TBI with a low fraction of 15 cGy to total doses of 75 to 150 cGy has been shown to be effective in about one-third of patients.

The paragraph beginning at page 22, line 1, is amended as follows:

A Phase II trial is currently being conducted by CALGB in CLL patients. ~~Rituximab®~~ rituximab and fludarabine are administered concurrently, followed by ~~Rituximab®~~ rituximab consolidation versus fludarabine induction followed by ~~Rituximab®~~ rituximab.

The heading beginning at page 22, line 4, is amended as follows:

~~Rituximab®~~ Rituximab with Myeloablative Therapy

The heading beginning at page 22, line 13, is amended as follows:

Retreatment of Relapsed Low-Grade NHL with ~~Rituximab®~~ rituximab

The paragraph beginning at page 22, line 14, is amended as follows:

A trial evaluating retreatment of 53 patients who had responded to ~~Rituximab®~~ rituximab and later relapsed has been reported (19). Seven of 56 evaluable patients (13%) obtained a CR and 16 a PR (29%), for an ORR of 52%. Four patients who had a second response received a third treatment; 3 of these responded.

The paragraph beginning at page 22, line 19, is amended as follows:

After treatment with two courses of ~~Rituximab®~~ rituximab, one patient's tumor, initially classified as follicular, small cleaved cell NHL, no longer expressed the CD20 antigen and was unresponsive to ~~Rituximab®~~ rituximab at the time of transformation to diffuse, large-cell NHL (20).

The paragraph beginning at page 22, line 23, is amended as follows:

Thus, while retreatment with ~~Rituximab®~~ rituximab is effective for treating patients who have relapsed after prior treatment with ~~Rituximab®~~ rituximab, there may be an increased incidence of CD20- tumor cells after secondary treatment. This observation supports the utility of the combined therapeutic regimens described herein.

The heading beginning at page 23, line 1, is amended as follows:

Combination of ~~Rituximab®~~ rituximab and CHOP Chemotherapy for Low-Grade NHL

The paragraph beginning at page 23, line 2, is amended as follows:

Chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is an effective first-line therapy for low-grade or follicular NHL. Though initial response rates are high, relapse eventually occurs and subsequent chemotherapy regimens produce remissions with shorter durations. A Phase II trial was initiated to evaluate the combination of CHOP and ~~Rituximab®~~ rituximab (21) in newly diagnosed and relapsed low-grade or follicular NHL because their mechanisms of action are not cross-resistant, and ~~Rituximab®~~ rituximab is synergistic with certain cytotoxic drugs, including doxorubicin (5).

The paragraph beginning at page 23, line 10, is amended as follows:

Twenty-nine of 38 patients received no prior anticancer therapy. CHOP was administered at standard doses every three weeks for six cycles with six infusions of ~~Rituximab®~~ rituximab (375 mg/m^2). ~~Rituximab®~~ rituximab infusions 1 and 2 were administered on Days 1 and 6 before the first CHOP cycle, which started on Day 8. ~~Rituximab®~~ rituximab infusions 3 and 4 were given 2 days before the third and fifth CHOP cycles, respectively, and infusions 5 and 6 were given on Days 134 and 141, respectively, after the sixth CHOP cycle.

The paragraph beginning at page 23, line 24, is amended as follows:

In a study to be conducted by CALGB, 40 patients with low-grade NHL will receive ~~Rituximab®~~ rituximab weekly times 8 and oral cyclophosphamide daily starting on Day 8. Twenty patients will receive ~~Rituximab®~~ rituximab alone for 8 weekly doses.

The heading beginning at page 24, line 8, is amended as follows:

Combination of ~~Rituximab®~~ rituximab with Cytokines

The heading beginning at page 24, line 9, is amended as follows:

~~Rituximab®~~ Rituximab plus interferon alpha

The paragraph beginning at page 24, line 14, is amended as follows:

In a combination trial, interferon-alpha (Roferon-A), a cytokine with a single-agent clinical activity in NHL (28), and ~~Rituximab®~~ rituximab were given to patients with relapsed low-grade or follicular NHL. Interferon-alpha (2.5 or 5 MIU) was administered subcutaneously, three times weekly for 12 weeks. ~~Rituximab®~~ Rituximab was administered by IV infusion weekly for four doses (375 mg/m^2) starting on the fifth week of treatment.

The ORR was 45% (17/38 patients); 11% had a CR and 34% had a PR. Kaplan-Meier estimates of the median DR and TTP in responders were 22.3+ and 25.2+ months, respectively (29). Previous combination studies of interferon-alpha and chemotherapeutic regimens containing anthracyclines yielded prolonged time to progression, but did not consistently increase response or survival rates (30-32). These early results suggest that the combination of ~~Rituximab®~~ rituximab and interferon-alpha may prolong the time to progression relative to ~~Rituximab®~~ rituximab alone.

The heading beginning at page 25, line 1, is amended as follows:

~~Rituximab®~~ Rituximab plus G-CSE

The paragraph beginning at page 25, line 2, is amended as follows:

In a separate study, ~~Rituximab®~~ rituximab and G-CSF are being evaluated in relapsed low-grade NHL. It has been demonstrated in vitro as well as in vivo in healthy volunteers that G-CSF, via its effect on myeloid precursor cells, induces FcRI-positive neutrophils that are capable of functioning as effector cells in ADCC. Therefor, a Phase I/II study was initiated to evaluate the toxicity and efficacy of the combined treatment.

The paragraph beginning at page 25, line 8, is amended as follows:

Both in Phase I and Phase II, patients were administered a standard dose of G-CSF (5 μg/kg/day) administered for three days, starting 2 days before administration of ~~Rituximab®~~ rituximab. Phase consisted of a dose escalation of ~~Rituximab®~~ rituximab (125, 250, or 375 mg/m^2 weekly X4). Early results in 9 patients evaluated so far yielded an ORR of 67% (44% CR, 22% PR) with minor toxicity in 8 of the 9 patients (33). The most frequent adverse events were fever (4/8 patients), rhinitis (4/8), chills (3/8) and headaches (3/8), which were comparable to the adverse events observed previously in administration of ~~Rituximab®~~ rituximab alone. The Phase II part of the study has been initiated, which will examine the efficacy of the combination of G-CSF and 375 mg/m^2 ~~Rituximab®~~ rituximab X4.

The heading beginning at page 25, line 18, is amended as follows:

~~Rituximab®~~ Rituximab plus IL-2

The paragraph beginning at page 28, line 3, is amended as follows:

Given the encouraging data gathered from single therapy studies with IL-2 on ABMT transplant recipients, it seemed reasonable to combine IL-2 therapy with ~~Rituximab®~~

rituximab post transplant, given that ~~Rituximab's~~ rituximab's biological activity appears to be mediated through ADCC and complement-mediated lytic activity. Thus, a Phase I trial has been initiated in collaboration with the FHCRC to evaluate the safety and potential efficacy of a combined therapeutic regimen.

The paragraph beginning at page 28, line 9, is amended as follows:

A separate Phase II study is also being performed to evaluate the efficacy and the incidence of HACA formation in patients receiving low-dose IL-2 and ~~Rituxan®~~ RITUXAN®. A specific objective of the study is to assess whether ADCC is enhanced by in vivo exposure to IL-2 and whether ADCC activity correlates with clinical response. Inclusion criteria for patients are histologically confirmed stage II-IV low-grade, follicular B-cell or mantle cell ylmphoma Inclusion criteria for patients are histologically confirmed stage II-IV low-grade, follicular B-cell or mantle cell ~~ylmphoma~~ lymphoma. Mantle cell lymphoma, for the purposes of this clinical study, is defined as CD5+, CD23- (if available) and/or bcl-1+ immunohistochemistry. Patients who did not respond to or have relapsed following their first treatment with a standard therapy, i.e., chemotherapy, radiotherapy, AMBT and/or immunotherapy, are eligible.

The heading beginning at page 28, line 19, is amended as follows:

~~Rituximab®~~ Rituximab plus GM-CSF for the Treatment of Relapsed Low Grade or Follicular B-Cell Lymphoma

The paragraph beginning at page 28, line 21, is amended as follows:

Two separate Phase II trials have also been initiated to test the efficacy of combined treatment with ~~Rituximab®~~ rituximab and GM-CSF. One study involves 40 patients with relapsed low grade B-cell lymphoma, and comprises administering ~~Rituximab®~~ rituximab weekly at 375 mg/m^2 weekly X 4 (d. 1, 8, 15, 22) and GM-CSF (Leukine, Immunex) at 250 mcg sc three times weekly for 8 weeks, starting one hour before the first dose of ~~Rituximab®~~ rituximab. This study will be used to evaluate the clinical efficacy (overall response rate (ORR), overall complete response rate, time to progression and failure-free survival) of the combined therapeutic regiment, to characterize the safety (qualitative, quantitative, duration and reversability of adverse events) of the combined therapy, and to determine the effects of the combined therapy on relevant lymphocyte subsets and cytokines. The second study plans to also monitor immunologic parameters to assess the mechanism of killing (complement C3

and C4, CH50, flow cytometry for CD3, CD4, CD8, CD16, CD19 and CD56 and ADCC assay).

The heading beginning at page 29, line 8, is amended as follows:

~~Rituximab®~~ Rituximab plus Gamma-Interferon

The paragraph beginning at page 29, line 9, is amended as follows:

Gamma-interferon may also be useful in combined therapy with ~~Rituximab®~~ rituximab for treating patients with low-grade or higher-grade lymphomas. It ~~is~~ has recently been found that gamma-interferon upregulates CD20 expression on multiple myeloma (MM) patient plasma cells, patient B-cells, as well as on normal donor B-cells (Treon et al., Lugano, 1999). In fact, Treon and colleagues have shown that gamma-interferon augments binding of these cells to ~~Rituximab®~~ rituximab. Induction of CD20 expression on plasma cells occurred in a dose dependent manner, with upregulation seen with as little as 1 U/ml of interferon gamma. A plateau occurred at 100 U/ml at 48 hours. Thus, gamma-interferon may also be beneficial when administered in combination with ~~Rituximab®~~ rituximab.

The paragraph beginning at page 29, line 21, is amended as follows:

In a study conducted in Europe and Australia, alternative dosing schedules were evaluated in 54 relapsed or refractory intermediate- or high-grade NHL patients (34). ~~Rituximab®~~ Rituximab was infused at 375 mg/m^2 weekly for 8 doses or at 375 ~~mg/m2~~ mg/m^2 once followed by 500 mg/m^2 weekly for 7 doses. The ORR was 31%; (CR 9%; PR 22%) no significant difference between the dosage regimens was observed. Patients with diffuse large-cell lymphoma (N = 30) had an ORR of 37% and those with mantle-cell lymphoma (N = 12) has an ORR of 33%

The heading beginning at page 30, line 1, is amended as follows:

Combination of ~~Rituximab®~~ rituximab and CHOP Chemotherapy

The paragraph beginning at page 30, line 2, is amended as follows:

In another study, 31 patients with intermediate- or high-grade NHL (19 females, 12 males, median age 49) received ~~Rituximab®~~ rituximab on Day 1 of each of six 21 -day cycles of CHOP (35). Of 30 evaluable patients, there were 19 CR (63%) and 10 PR (33%), for an ORR of 96%. This regimen was considered well tolerated and may result in higher response rates than with ~~Rituximab®~~ rituximab or CHOP alone.

The paragraph beginning at page 30, line 8, is amended as follows:

The NCI Division of Cancer Treatment and Diagnosis is collaborating with IDEC Pharmaceuticals Corporation to explore ~~Rituximab®~~ rituximab treatment in other indications. A Phase II trial of CHOP versus CHOP and ~~Rituximab®~~ rituximab is being conducted by ECOG, CALGB, and SWOG in older patients (> 60 years) with mixed, diffuse large cell, and immunoblastic large cell histology NHL (N = 630 planned). This study includes a secondary randomization to maintenance with ~~Rituximab®~~ rituximab versus non-maintenance.

The paragraph beginning at page 30, line 15, is amended as follows:

A Phase III trial of ~~Rituximab®~~ rituximab and CHOP in 40 patients with previously untreated mantle-cell lymphoma is also ongoing at the Dana Farber Institute. ~~Rituximab®~~ Rituximab is administered on Day 1 and CHOP is given on Days 1 - 3 every 21 days for 6 cycles. Accrual for this study has been completed. A Phase II trial of CHOP followed by ~~Rituximab®~~ rituximab in newly diagnosed follicular lymphoma conducted by SWOG has also been completed. Results of these two trials are being analyzed.

The paragraph beginning at page 30, line 22, is amended as follows:

A Phase II trial of CHOP and ~~Rituximab®~~ rituximab versus CHOP alone in HIV-related NHL conducted by the AIDS Malignancy Consortium is ongoing; 120 patients are planned.

The heading beginning at page 30, line 25, is amended as follows:

~~Rituximab®~~ Rituximab after Myeloablative Therapy Relapse

The paragraph beginning at page 30, line 26, is amended as follows:

~~Rituximab®~~ Rituximab has shown promising early results in patients with relapsed intermediate-grade NHL after high-dose therapy with autologous PBSC support. Six of seven patients responded (1 CR and 5 PR) and one patient had stable disease; therapy was well tolerated (36).

The paragraph beginning at page 31, line 4, is amended as follows:

Adverse events and clinical laboratory data from 315 patients in the five single-agent U.S. studies were combined to provide a safety profile of ~~Rituximab®~~ rituximab in patients with low-grade or follicular NHL. The majority of adverse events were infusion-related and occurred with decreasing frequency after the first infusion. The most common infusion-

related events were fever (49%), chills (43%), nausea (18%), fatigue (16%), headache (14%), andioedema (13%), pruritus (10%), and occasionally, hypotension (10%) and bronchospasm (8%). During the treatment period (up to 30 days following the last dose), 10% of patients experienced Grade 3 or 4 adverse events, which were primarily infusion-related or hematologic. Thrombocytopenia (< 50,000 platelets/mm^3) occurred in 1.3% of patients, neutropenia (<1000/mm^3) occurred in 1.9%, and anemia (< 8 gm/dL) occurred in 1.0%. Although ~~Rituximab®~~ rituximab induced B-cell depletion in 70% - 80% of patients, abnormally decreased serum immunoglobulins were observed in a minority of patients and the incidence of infection did not appear to be increased.

The paragraph beginning at page 31, line 19, is amended as follows:

Hypotension requiring interruption of the ~~Rituximab®~~ rituximab infusion occurred in 10% of patients and was Grade 3 or 4 in 1%. Andioedema was reported in 13% of patients and was considered serious in one patient. Bronchospasm occurred in 8% of patients; 2% were treated with bronchodilators. A single report of bronchiolitis obliterans was noted. Most patients experienced no further infusion-related toxicities by the second and subsequent infusions. The percentage of patients reporting adverse events upon retreatment was similar to that reported following the first course (14).

The paragraph beginning at page 32, line 1, is amended as follows:

Four patients developed arrhythmias during ~~Rituximab®~~ rituximab infusion. One of the four discontinued treatment because of ventricular tachycardia and supraventricular tachycardias. The other three patients experienced trigeminy (N = 1) and irregular pulse (N = 2) and did not require discontinuation of therapy. Angina was reported during infusion and myocardial infarction occurred four days postinfusion in one subject with a prior history of myocardial infarction.

The paragraph beginning at page 32, line 13, is amended as follows:

Since FDA of ~~Rituximab®~~ rituximab for treatment of relapsed or refractory low-grade or follicular NHL in 1997, an estimated 17,000 patients have been treated. In May, 1998, descriptions of eight post-marketing reports of severe infusion-related adverse effects associated with the use of ~~Rituximab®~~ rituximab that resulted in fatal outcomes were summarized. In seven of the eight fatalities, severe symptoms occurred during the first ~~Rituximab®~~ rituximab infusion. The cause of death was not reported or remains unknown

for two of the eight cases. Severe respiratory events, including hypoxia pulmonary infiltrates, or adult respiratory distress syndrome contributed to six of the eight reported deaths. One patient had a pretreatment lymphocyte count of 600,000 mm^3; another, a creatinine of 8; a third, a respiratory rate of 40; and a fourth, pancytopenia. Patients with a high tumor burden or with a high number of circulating malignant cells may be at higher risk and these patients should be monitored closely throughout each infusion.

The paragraph beginning at page 33, line 1, is amended as follows:

Most of the adverse events recently described were previously observed in ~~Rituximab®~~ rituximab clinical studies. One notable exception is an infusion-related syndrome associated with rapid tumor lysis, that was reported in six patients with high numbers of circulating tumor cells (37, 38). This syndrome was characterized by fever, rigors, bronchospasm with associated hypoxemia, a rapid decline in peripheral lymphocytes, laboratory evidence of tumor destruction, and transient, severe thrombocytopenia. These patients had diagnoses of B- prolymphocytic leukemia (N = 2), chronic lymphocytic leukemia (N = 2), mantle-cell lymphoma (N = 1), or transformed NHL (N = 1); all had elevated circulating lymphocytes, bulky adenopathy, and organomegaly. Although five of these six patients required hospitalization, symptoms resolved and subsequent ~~Rituximab®~~ rituximab treatments were well tolerated; the last patient refused further therapy and died of progressive disease two week later.

The paragraph beginning at page 33, line 14, is amended as follows:

In a separate report of seven patients with CLL and one patient with mantle-cell lymphoma, tumor lysis syndrome was observed after the first ~~Rituximab®~~ rituximab infusion in those patients with lymphocyte counts > 10 x 10^9L (39).

The heading beginning at page 33, line 17, is amended as follows:

RADIOIMMUNOTHERAPY WITH ^{90}YTTRIUM-LABELED ANTI-CD20 ANTIBODY IN COMBINATION WITH ~~RITUXIMAB®~~ RITUXIMAB

The paragraph beginning at page 33, line 19, is amended as follows:

Another therapeutic approach to NHL under evaluation is a radiolabeled anti-CD20 antibody (IDEC-Y2B8) in combination with ~~Rituximab®~~ rituximab. IDEC-Y2B8 (^{90}Y-ibritumomab tiuxetan) is a murine IgG_1 kappa anti-CD20 antibody conjugated to ^{90}Y via a chelator, MX-DTPA, which is covalently bound to the antibody. ~~Rituximab®~~ Rituximab

(250 ~~mg/m2~~ mg/m^2) is administered prior to IDEC-Y2B8 to deplete peripheral B lymphocytes and improve biodistribution of the radiolabeled antibody.

The paragraph beginning at page 34, line 7, is amended as follows:

A Phase III randomized study comparing IDEC-Y2B8 with ~~Rituximab®~~ rituximab (375 mg/m^2 weekly times 4) for treatment of low-grade follicular or transformed NHL patients is ongoing. Another Phase III trial is also being conducted in patients with relapsed NHL who are refractory to ~~Rituximab®~~ rituximab.

The paragraph beginning at page 34, line 12, is amended as follows:

In the absence of curative therapy for NHL, the object of treatment is to achieve control of the disease for a meaningful duration and provide relief to tumor related symptoms without undue toxicity. Treatment with ~~Rituximab®~~ rituximab is a brief, 22-day outpatient therapy with limited adverse events in most patients. In clinical studies, 50% of evaluable relapsed or chemotherapy refractory low-grade or follicular NHL patients achieved complete or partial responses. These responses were durable without maintenance therapy; the median TTP for responders was 13.2 months and the median DR was 11.6 months in the pivotal study.

The paragraph beginning at page 34, line 21, is amended as follows:

~~Rituximab®~~ Rituximab is approved as a safe and effective treatment for patients with relapsed low-grade or follicular B-cell NHL. It has significant clinical activity, a novel mechanism of action, and compares favorably with alternative therapies in response rate and response duration. Completion of ongoing studies will verify the role of alternative ~~Rituximab®~~ rituximab regimens and ~~Rituximab®~~ rituximab in the treatment of other CD20+ B-lymphocyte malignancies.

The paragraph beginning at page 35, line 21, is amended as follows:

7. Maloney D, Grillo-López A, White C, Bodkin D, Schilder R, Neidhart J, Janakiraman N, Foon K, Liles T-M, Dallaire B, Wey K, Royston K, Davis T, Levy R. IDEC-C2B8 (~~Rituximab®~~ rituximab) anti-CD20 anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. *Blood* 1997; 90:O 2188-2195.

The paragraph beginning at page 35, line 26, is amended as follows:

8. McLaughlin P, Grillo-López A, Link B, Levy R, Czuczman M, Williams M, Heyman M, Bence-Bruckler I, White C, Cabanillas F, Jain V, Ho A, Lister J, Wey K, Shen D, Dallaire B. ~~Rituximab®~~ Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients response to a 4-dose treatment program. Journal of Clinical Oncology 1998; 16:2825-2833.

The paragraph beginning at page 36, line 22, is amended as follows:

13. Piro L, White C, Grillo-López A, Janakiraman N, Saven A, Beck T, Varns C, Shuey S, Czuczman M, Lynch J, Kolitz J, Jain V. Extended ~~Rituxan~~ rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. 1999; Submitted